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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/954,483	SIEBEL ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-31* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-26 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 2/17/2004, in which claims were amended (claims 1, 8, 18, 20-26, 29-31) and in which claim 11 was cancelled. Claims 1-10, 12-31 are pending in the instant application, with claims 27-28 withdrawn from consideration as being directed to a nonelected invention.

Any rejection of record in the office action mailed 8/11/2003 not addressed herein is withdrawn. This action is not final as there are new grounds of rejection presented herein that were not necessitated by applicants' amendment of the claims in the response filed 2/17/2004.

Sequence Compliance

Receipt is acknowledged of applicants' submission on 2/17/2004 of a paper copy of the sequence listing, CRF and corresponding attorney's statements concerning the content of the submitted documents. The application is now in sequence compliance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12-26 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. **This rejection is maintained for reasons of record in the office action mailed 8/11/2003 and repeated below. The grounds of rejection are extended to amended claim 26 as claim 26 comprises embodiments where the targeting vector of claim 1 has been inserted into the target chromosome via random integration.**

Each of the claims features a targeting construct comprising a positive selection marker, two regions of homology to a target sequence and a "regulator" that controls expression of the positive selection marker. The specification describes the regulator as being "...a sequence or sequences (i.e. polynucleotide sequence or protein sequence) that regulates or controls expression of the selectable marker..." (page 8, lines 15-18). The specification also teaches that the regulator functions to down regulate expression of the selectable marker on the targeting construct when the construct is randomly incorporated into the target genome by illegitimate recombination events (e.g. pages 5-6, bridging paragraphs). This allows the skilled artisan to select for the presence of the positive selection marker and reduce the number of false-positives for proper incorporation of the targeting construct into the target sequence due to the reduced expression of the marker in those cells where the marker is randomly incorporated. Due to this feature, the skilled artisan does not need to utilize negative selection methodologies. The rejected claims encompass an enormous genus of targeting constructs comprising a "regulator" comprising literally any protein or DNA sequence, or combination thereof, arranged in any fashion on the targeting construct. The "regulator" must function, however, to down regulate expression of the positive selection marker if the targeting construct does not insert into the target sequence.

The specification describes a single relevant working example where the two sequences with homology to the target sequence flank a selectable marker cassette and where a gene encoding a transcriptional repressor (lacI) is located on the construct on the other side of one of the two targeting sequences from the positive selection marker (e.g. neo^r). The gene encoding the selectable marker in this case is under the control of a promoter comprising the cognate operator sequence (lacO) for the repressor such that, if random incorporation of the entire targeting construct into the host genome occurs, expression of the positive selection marker is repressed. A double crossover event between the targeting sequences on the construct and the target sequence in the genome, however, results in the release of at least part of the "regulator" and allows more efficient expression of the selectable marker. No other arrangement of the different components of the targeting constructs is described in the instant specification. For example, no description is provided for an alternate arrangement of the two regions of homology to the target sequence and the positive selection marker. The specification asserts that a transcriptional silencer element (e.g. NRF, COL4, etc.) could also work in *cis* to accomplish the same effect, but no arrangement of such an element has been described in the instant specification. Thus, the instant specification does not provide a basis for one of skill in the art to envision a sufficient number of other arrangements of the recited elements to describe the broadly claimed targeting vectors embraced by the rejected claims.

The prior art does not appear to teach a system of utilizing a "regulator" to down regulate expression of a positive selection marker in targeting constructs when the constructs are randomly inserted into the genome of a host cell. Therefore, the prior art does not offset the deficiencies of the instant specification concerning a basis for one to envision a number of

alternative arrangements of the recited elements or other types of regulators sufficient to describe the broadly claimed genus.

Given that the term "regulator" apparently encompasses a huge number of possible DNA sequences and proteins sequences, or combinations thereof, and given the functional limitations of what the "regulator" must accomplish, the skilled artisan would not be able to envision a sufficient number of embodiments of the claimed invention to describe the broadly claimed genus of targeting vectors. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the claimed invention at the time of filing.

Response to Arguments

Applicant's arguments filed in the response of 2/17/2004 have been fully considered but they are not persuasive. The response essentially argues: 1) the amendment to the claims more clearly defines the organization of the "regulator" in the targeting construct of the claims and makes clear the structural/functional properties of the regulator, and 2) pages 12-14 provide many examples of regulators and selectable markers.

A single embodiment where a selectable marker is put under the control of a bacterial repressor/operator binding site cannot be considered as providing sufficient structural/functional correlation such that the skilled artisan could envision a sufficient number of other embodiments to describe the broadly claimed genus of regulator/selectable marker constructions. As indicated in making the rejection, the recitation of elements that might be usable together provided by the specification does not provide a structural/functional basis for the skilled artisan to envision those embodiments that would actually function in the manner described in the specification for the targeting constructs of the invention. For example, not a single actual embodiment, prophetic

or otherwise, is described where a transcriptional silencer is the regulator and present in a construct as currently claimed with a particular selectable marker and particular targeting sequences. In addition, the term "regulator" encompasses other embodiments where the "regulator" is not a bacterial repressor or transcriptional silencer (e.g. a transcriptional anti-terminator, a ribozyme specific for the selectable marker, etc.). For these reasons, the skilled artisan would not have been able to envision a sufficient number of specific "regulator"/targeting sequence/selectable marker combinations to describe the broadly claimed genus of constructs bearing these elements.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 and 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of the claims recites a limitation of a "regulator". **This rejection is maintained for reasons of record in the office action mailed 8/11/2003 and repeated here.** The metes and bounds of this term are unclear in the context of the claimed invention. The specification describes the regulator as being "...a sequence or sequences (i.e. polynucleotide sequence or protein sequence) that regulates or controls expression of the selectable marker..." (page 8, lines 15-18). The specification also teaches that the regulator functions to down regulate expression of the selectable marker on the targeting construct when the construct is randomly incorporated into the target genome by illegitimate recombination events (e.g. pages 5-6, bridging

paragraphs). It is unclear how a regulator can be comprised within a targeting vector and also be a protein. Also, it is unclear whether the term necessarily refers to protein and nucleic acid sequences in certain embodiments. For example, in the embodiment exemplified in the instant specification (e.g. in Figure 5), the targeting vector comprises an operator sequence (lacO) operatively linked to the promoter that drives the selectable marker, as well as a sequence encoding the lac repressor (lacI). In this case, does the term "regulator" refer to the cis-acting lacO sequence, the coding sequence for lacI or the repressor protein; or does it necessarily refer to a combination of all three? It would be remedial to amend the claim language to make clear which elements, protein or DNA sequence or both, must be present in order for a targeting construct to satisfy the limitation of comprising a "regulator".

Response to Arguments/112 2nd Paragraph

Applicant's arguments filed 2/17/2004 have been fully considered but they are not persuasive. The response essentially argues: the amendment of the claims makes clear what is claimed.

This assertion is not accurate. For example, it remains unclear how a protein can be comprised within the targeting construct as recited. Yet, dependent claims (e.g. claims 12-13) still recite the limitation that the regulator comprises at least one repressor sequence (e.g. a protein?). Therefore, it remains unclear exactly what is being claimed (i.e. a protein coding sequence or a cis-acting structure such as a transcriptional silencer element).

The following are new rejections.

Claim 1 is vague and indefinite in that there is no clear and positive prior antecedent basis in the claim for the term "the target gene".

Claims 12 and 13 recite the limitation "wherein the regulator comprises at least one repressor sequence". It is unclear whether the term "repressor sequence" refers to a coding sequence for a repressor (e.g. the lac repressor), the amino acid sequence of the repressor itself or a repressor binding sequence (e.g. the lac operator). Based upon the positioning of the regulator in the targeting construct it appears the term is intended to specify a repressor coding sequence. It would be remedial to amend the claim to clearly indicate which of the three possibilities is intended.

Claims 20, 22, 29-30 are vague and indefinite in that there is no clear and positive prior antecedent basis for the phrase "the regulator controls expression of a selectable marker" (examiner's emphasis added). It would be remedial to amend the claims by substituting the word "the" for "a" so that the claims read "the selectable marker".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 26 is rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi et al (AC; U.S. Patent No. 5,627,059; see the entire patent). **This rejection is maintained for reasons of record in the office action mailed 8/11/2003 and repeated below.**

Claim 26 is drawn to an isolated host cell comprising a modification or disruption of a target gene, wherein the target gene is modified or disrupted by insertion of a targeting vector into the host cell.

Capecchi et al teach the use of positive-negative targeting vectors that comprise targeting sequences flanking a positive selection marker and which further comprise a negative selection marker outside of the targeting cassette that allows for selection against random insertion events (e.g. Abstract; Figure 1). The '059 patent teaches examples where particular genes in a target cell have been inactivated by insertion of a targeting construct (e.g. Example 4-Disruption of the hox1.4 locus in mouse ES cells).

Response to Arguments/35 U.S.C. 102(b)-Capecchi et al

Applicant's arguments filed 2/17/2004 have been fully considered but they are not persuasive. The response essentially argues: the amendment of the claim to depend on claim 1 obviates the rejection as Capecchi et al have not taught the vector of claim 1. This argument is not persuasive due to the fact that if applicants' vector works as it is supposed to function, and the "regulator" does not function by binding to some element of the selectable marker (e.g. it is a "cis-acting" element such as a transcriptional silencer), then the resulting disrupted gene would be essentially indistinguishable from that taught by Capecchi et al due to the absence of any regulator element in the disrupted gene.

Claims 1, 18, 20, 29-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuebler et al (J. Mol. Biology, Vol. 281, pages 803-814; see the entire reference). **This is a new rejection.**

It is noted that the term "selectable marker cassette" is not explicitly defined in the instant specification and can be interpreted broadly to encompass any selectable trait that is, as recited by the claims, flanked by targeting sequences.

Kuebler et al teach the construction of a vector, pDK H436am, which comprises a gene encoding a mutant form of the T4 terminase (i.e. gp17) under control of the T7 RNA polymerase promoter (i.e. a "regulator" of expression of the selectable marker) of pET 9D (e.g. column 2, page 807). In this case, the "selectable marker cassette" is the H436am mutation, which comprises sequences on either side of it homologous to gene 17 of the wildtype phage. Kuebler et al cross the H436am mutation into a 17amK166 phage to generate recombinant phage comprising the selectable H436am mutation and lacking the 17amK166 mutation (i.e. 17amK166 mutants are unable to replicate in the genetic background used for selection). Recombinant phage were then selected based upon their ability to grow on the His suppressor background but not on the equivalent suppressor minus strain of E. coli (e.g. page 807, second full paragraph of column 2).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Examiner
Art Unit 1636

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PRIMARY EXAMINER